Cancer Mortality in Agricultural Regions of Minnesota

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Because of its unique geology, Minnesota can be divided into four agricultural regions: south-central region one (corn, soybeans); west-central region two (wheat, corn, soybeans); northwest region three (wheat, sugar beets, potatoes); and northeast region four (forested and urban in character). Cancer mortality (1980–1989) in agricultural regions one, two, and three was compared to region four. Using data compiled by the National Center for Health Statistics, cancer mortality was summarized by 5-year age groups, sex, race, and county. Age-standardized mortality rate ratios were calculated for white males and females for all ages combined, and for children aged 0–14. Increased mortality rate ratios and 95% confidence intervals (CIs) were observed for the following cancer sites: region one—lip (men), standardized rate ratio (SRR) = 2.70 (CI, 1.08–6.71); nasopharynx (women), SRR = 3.35 (CI, 1.20–9.31); region two—non-Hodgkin's lymphoma (women), SRR = 1.35 (CI, 1.09–1.66); and region three—prostate (men), SRR = 1.12 (CI, 1.00–1.26); thyroid (men), SRR = 2.95 (CI, 1.35–6.44); bone (men), SRR = 2.09 (CI, 1.00–4.34); eye (women), SRR = 5.77 (CI, 1.90–17.50). Deficits of smoking-related cancers were noted. Excess cancers reported are consistent with earlier reports of agriculturally related cancers in the midwestern United States. However, reports on thyroid and bone cancer in association with agricultural pesticides are few in number. The highest use of fungicides occurs in region three. Ethylenebisdithiocarbamates, whose metabolite is a known cause of thyroid cancer in rats, are frequently applied. This report provides a rationale for evaluation of the carcinogenic potential of this suspect agent in humans. *Key words:* agriculture, cancer mortality, fungicides, herbicides, human, pesticides, rural population. *Environ Health Perspect* 106:205–211 (1999). [Online 2 February 1999]
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In Minnesota, major differences in agricultural practices, including crop production, pesticide use, and other land use are based on regional differences in ecology and geology. Northeastern Minnesota is forested with a volcanic rock base. Southern and south-central Minnesota is a rolling, limestone based region that forms the transition between forest and prairie. Western and northwestern Minnesota is a northern tall grass prairie region formed on a large, flat, glacial-clay lake bed (the Red River Valley of the North) and extending into Canada (*1*).

Based on information from the Minnesota Extension Service (St. Paul, MN), Minnesota can be divided into three major crop-growing regions: region one (south and south-central Minnesota) grows corn and soybeans; region two (western Minnesota) grows wheat, corn, and soybeans; and region three (northwestern Minnesota) produces wheat, sugar beets, and potatoes (Fig. 1) (*2*). Region four includes the forested regions of northeastern Minnesota and the major urban population centers of Minneapolis/St. Paul and Duluth. Pesticide use differs by crop and crop-growing region (*3*). In regions two and three, fungicides and chlorophenoxy herbicides are extensively used, with aerial pesticide applications being common. In region one, groundwater contamination from pesticides and nitrates has been observed; this contamination is rare in regions two and three (*4,5*). In addition, region one is the major beef- and hog-producing area of Minnesota (*6*). Clearly, the diverse geologic and ecologic features of Minnesota impact pesticide use and groundwater contamination. These differences also offer a unique opportunity to explore possible environmental toxicant effects in a relatively homogenous population.

In an earlier study we reported increased birth defects in the crop regions of Minnesota, especially in regions two and three, as compared to referent region four, not only in the offspring of private pesticide appliers, but also in the offspring of the general population (*7*). Within each of the four regions, the offspring of private pesticide appliers had a higher birth defect rate than the offspring of the general population. These results prompted us to explore the possibility that other health end points such as cancer might provide further insight into these initial observations. In particular, we were interested to see whether mortality for some cancers, e.g., cancers of the endocrine system, might parallel the birth defect rate and show higher rates in regions two and three (*8*).

The objective of the current study is to investigate whether cancer mortality as the underlying cause of death is increased among residents of each of the three agricultural regions with heavy use of pesticides, as compared to residents of the major urban/forested region of the state with low use of pesticides.

Many studies have addressed the association between cancer in humans and agricultural pesticide exposure. Both occupational pesticide exposures (e.g., farmers, pesticide mixers, and appliers) and nonoccupational exposures occur. Examples of nonoccupational exposures include those among families of farmers exposed to pesticides stored at the house, to contaminated clothing, and to household dust containing pesticides, or exposures among residents of agricultural communities exposed to contaminated ground and surface water, to contaminated soil, or to drift from aerial spraying of pesticides. Mortality and incidence studies of male and female agricultural workers have reported slightly increased rates for the following cancers: non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, leukemia, lip, eye, stomach, melanoma, other skin cancer, prostate, testis, ovary, breast, brain, and soft-tissue sarcoma (*9–11*). Children of parents who work in agriculture may be a susceptible subgroup, and may have increased risk for cancers such as leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, soft-tissue sarcoma, and cancers of the brain, eye, and central nervous system (*12–14*).

Ecological studies have reported on the association between living in an agricultural region and cancer incidence. A study of residents in a midwestern rural farming community reported significant increases in the incidence of lymphoproliferative cancers,

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which may have resulted from sustained environmental exposures to agricultural chemicals (*15*). Another study investigating the association between breast cancer and exposure to atrazine in Kentucky counties reported a significant increase in breast cancer risk for high atrazine exposure (*16*). A surrogate measure for pesticide exposure in these studies was the acreage of planted or treated crops or the contamination of ground and surface water by pesticides. In ecologic studies the exposure is measured for communities or counties, but not for individual subjects. The best use of these studies is to generate, rather than to test, hypotheses in a cost-efficient manner. Although definitive conclusions cannot be drawn, well-focused confirmatory epidemiologic and laboratory studies can be formulated based on studies such as these.

Materials and Methods

Cancer mortality data. Cancer mortality data (underlying cause of death) for 1980–1989, as collected by the National Center for Health Statistics (NCHS), were summarized for 34 cancer sites by 5-year age groups (0–4, 5–9, ..., 80–84, 85+), sex, race, county, and state of residence. This summarization was based on methods used by the National Cancer Institute to summarize cancer mortality for 1950–1959, 1960–1969, and 1970–1979 (*17*). Occupational information was not available in this dataset. Population data for 1980–1989 by county of residence, race, sex, and 5-year age groups were obtained from 1980 and 1990 census data; the annual midyear populations were estimated by interpolation between census years. Estimates for the total population at risk during 1980–1989 were obtained by combining the population at risk over the individual years.

Agricultural regions and pesticide use. A 1990 survey conducted by the Minnesota Department of Agriculture provided detailed information on crop production, acreage, and pesticide use by county cluster (*3*). Minnesota's 87 counties are distributed over 25 county clusters based on similarity of geology and crops; each cluster consists of at least two adjoining counties. Pesticide use was estimated from >12,000 questionnaires received from agricultural farmers in the 25 county clusters (*3*). The most often used herbicides are 2,4-dichlorophenoxyacetic acid, (4-chloro-2-methylphenoxy)acetic acid, and other chlorophenoxy herbicides (wheat, corn), alachlor (corn, soybean), atrazine (corn), bentazon (soybean), bromoxynil (wheat, corn), cyanazine (corn), dicamba (corn), *S*-ethyl dipropylthiocarbamate (corn), imazethapyr (soybean), metolachlor (corn),

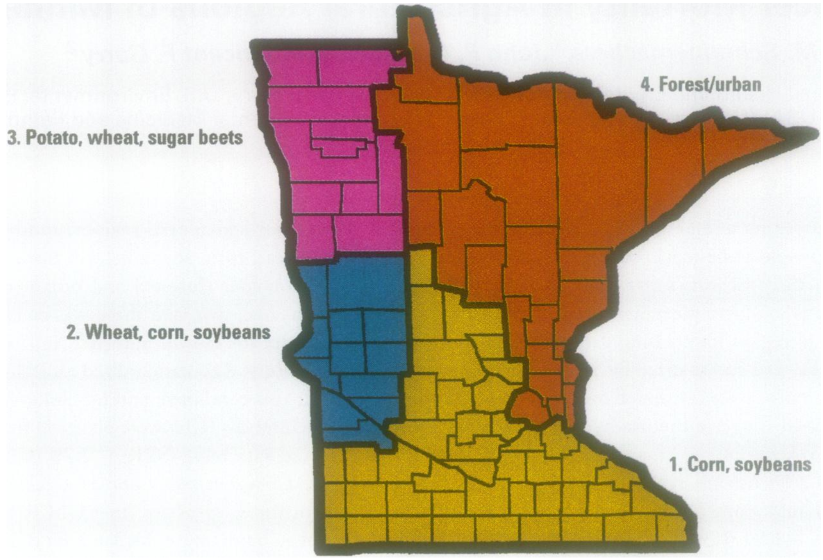

Figure 1. Major crop-growing regions of Minnesota. Regions differ by major crops, pesticide use, geology, and ecology. Region two is the transition zone between the corn/soybean and wheat-producing regions. The metropolitan area is located in the southern part of region four, the reference region for this study.

Table 1. Cancer mortality rate ratios for white males during 1980–1989, comparing agricultural regions one, two, and three to region four[a]

	Region four		Agricultural regions			
Cancer site (*ICD-9* code)	Count	Rate	Region	Count	Rate	SRR (CI)
Lip (140)	7	0.07	1	14	0.18	2.70 (1.08–6.71)**
Salivary gland (142)	30	0.30	1	13	0.17	0.58 (0.30–1.13)
Nasopharynx (147)	26	0.25	1	24	0.35	1.39 (0.79–2.42)
Oral cavity, including tongue	365	3.62	1	170	2.33	0.64 (0.54–0.77)*
(141,143–146, 148, 149)			2	32	2.56	0.71 (0.49–1.03)
			3	29	2.93	0.81 (0.55–1.19)
Esophagus (150)	556	5.53	1	318	4.35	0.79 (0.68–0.90)*
			2	53	4.31	0.78 (0.58–1.05)
			3	46	4.12	0.74 (0.55–1.01)
Stomach (151)	759	7.50	1	540	7.04	0.94 (0.84–1.05)
			2	106	7.38	0.98 (0.80–1.21)
			3	85	7.23	0.96 (0.76–1.22)
Large intestine (153, 159)	2,090	20.64	1	1,470	19.29	0.93 (0.87–1.00)*
			2	290	21.26	1.03 (0.91–1.17)
			3	229	19.51	0.95 (0.82–1.09)
Rectum (154, excluding 154.3)	385	3.81	1	276	3.72	0.98 (0.84–1.14)
			2	46	3.42	0.90 (0.65–1.23)
			3	50	4.27	1.12 (0.83–1.52)
Liver, gallbladder, including	486	4.80	1	282	3.74	0.78 (0.67–0.90)*
bile ducts (155, 156)			2	50	3.76	0.78 (0.58–1.06)
			3	34	2.85	0.59 (0.42–0.84)*
Pancreas (157)	1,093	10.81	1	656	8.83	0.82 (0.74–0.90)*
			2	125	9.41	0.87 (0.72–1.06)
			3	111	9.65	0.89 (0.73–1.09)
Nose, nasal cavities, middle ear, accessory sinuses (160)	19	0.18	1	21	0.29	1.58 (0.85–2.96)
Larynx (161)	226	2.24	1	108	1.47	0.66 (0.52–0.83)*
			2	17	1.33	0.59 (0.36–0.99)*
			3	15	1.39	0.62 (0.37–1.06)
Trachea, bronchus, lung	6,395	63.51	1	3,503	48.05	0.76 (0.73–0.79)*
(162, 163, 165)			2	580	44.67	0.70 (0.64–0.77)*
			3	526	48.45	0.76 (0.70–0.84)*
Breast (174, 175)	19	0.19	1	16	0.21	1.11 (0.57–2.16)
Prostate (185)	2,453	24.08	1	1,955	24.05	1.00 (0.94–1.06)
			2	380	23.89	0.99 (0.89–1.11)
			3	352	27.03	1.12 (1.00–1.26)**
Testis (186)	34	0.25	1	32	0.39	1.54 (0.94–2.52)
Kidney, ureter (189,	572	5.66	1	363	4.89	0.86 (0.76–0.99)*
excluding 189.3)			2	73	5.50	0.97 (0.75–1.25)
			3	66	5.93	1.05 (0.81–1.36)

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Table 1. *continued*

Cancer site (*ICD-9* code)	Region four Count	Region four Rate	Agricultural regions Region	Agricultural regions Count	Agricultural regions Rate	SRR (CI)
Bladder, other urinary organs (188, 189.3)	618	6.08	1	422	5.27	0.87 (0.76–0.98)*
			2	54	3.51	0.58 (0.44–0.77)*
			3	55	4.31	0.71 (0.54–0.94)*
Malignant melanoma (172)	247	2.38	1	177	2.43	1.02 (0.84–1.24)
			2	23	1.85	0.78 (0.50–1.21)
			3	16	1.57	0.66 (0.39–1.11)
Nonmelanoma skin (173, 154.3)	102	0.98	1	82	1.04	1.06 (0.79–1.42)
			2	9	0.68	0.69 (0.33–1.44)
			3	8	0.64	0.65 (0.31–1.36)
Eye (190)	13	0.13	1	11	0.15	1.18 (0.52–2.64)
Brain, other parts of nervous system (191, 192)	587	5.70	1	367	5.10	0.89 (0.78–1.02)
			2	62	5.53	0.97 (0.74–1.27)
			3	56	5.78	1.02 (0.77–1.34)
Thyroid (193)	26	0.25	1	11	0.15	0.60 (0.29–1.22)
			2	5	0.47	1.88 (0.69–5.10)
			3	9	0.73	2.95 (1.35–6.44)**
Thymus and other endocrine glands (194, 164.0)	33	0.34	1	19	0.26	0.76 (0.43–1.35)
			3	5	0.57	1.69 (0.65–4.44)
Bone, including jaw (170)	49	0.47	1	38	0.52	1.10 (0.72–1.70)
			2	5	0.50	1.06 (0.40–2.81)
			3	9	0.98	2.09 (1.00–4.34)**
Connective and soft tissue (171, 164.1)	137	1.33	1	61	0.81	0.61 (0.45–0.83)*
			2	10	0.84	0.63 (0.33–1.23)
			3	16	1.51	1.13 (0.67–1.93)
Hodgkin's disease (201)	114	1.01	1	77	1.02	1.01 (0.75–1.35)
			2	11	1.20	1.18 (0.62–2.26)
			3	6	0.50	0.50 (0.22–1.13)
Lymphosarcoma, reticulum cell sarcoma, including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	754	7.37	1	606	8.09	1.10 (0.99–1.22)
			2	86	6.47	0.88 (0.70–1.11)
			3	82	7.38	1.00 (0.79–1.27)
Multiple myeloma (203, excluding 203.1)	344	3.41	1	270	3.56	1.05 (0.89–1.23)
			2	52	3.70	1.08 (0.80–1.46)
			3	35	3.03	0.89 (0.62–1.27)
Leukemia (204–208, 202.4, 203.1)	900	8.78	1	710	9.32	1.06 (0.96–1.17)
			2	119	9.55	1.09 (0.89–1.33)
			3	116	10.10	1.15 (0.94–1.40)
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	1,342	13.24	1	788	10.34	0.78 (0.71–0.85)*
			2	134	10.00	0.76 (0.63–0.91)*
			3	124	10.98	0.83 (0.69–1.00)*
All cancers (140–208)	20,781	204.90	1	13,400	177.43	0.87 (0.85–0.89)*
			2	2,342	173.10	0.84 (0.81–0.88)*
			3	2,091	182.52	0.89 (0.85–0.93)*

Abbreviations: *ICD-9, International Classification of Diseases, 9th Revision* (World Health Organization, Geneva); SRR, standardized rate ratio; CI, 95% confidence interval. Rates per 100,000 are age-adjusted.

[a]Provided at least five deaths are reported in each of the two groups being compared.

*Significantly decreased SRR.

**Significantly increased SRR.

and trifluralin (soybean). Although reliable estimates of fungicide use in Minnesota are difficult to obtain, the 1990 survey (*3*) concluded that the largest amount of fungicides is applied aerially to crops in the northwestern part of the state. The most commonly used fungicides are supertin (potatoes, sugar beets, wheat), maneb (potatoes), mancozeb (potatoes, sugar beets, wheat), captan (potatoes), chlorothalonil (potatoes), blite-out (potatoes), triphenyltin (sugar beets), copper (sugar beets), benomyl (sugar beets), and propiconazole (wheat).

For the purpose of this study, we combined the 25 county clusters into four regions based on crops. Using information from the 1987 U.S. Department of Agriculture's agricultural census (*18*), the percentage of available land devoted to agriculture was estimated as 79% in region one, 81% in regions two and three, and 22% in referent region four.

Statistical analysis. Age-standardized mortality rate ratios (SRRs) comparing regions one, two, and three to region four were calculated by gender for all ages combined for each of the 34 cancer sites. SRRs were determined only if at least five deaths were reported for a subcategory. Only white males and females were included, because data were too sparse for nonwhites to allow reliable analysis. For significantly increased SRRs (or borderline significantly increased SRRs with the lower confidence limit = 1), additional SRRs were calculated for age categories <65 and ≥65. In addition, childhood cancer mortality was assessed for ages 0–14 because children are considered a susceptible subpopulation. The direct method used for standardization was based on the 1970 U.S. population (5-year age intervals). Confidence intervals were calculated using a method described by Rothman and Greenland, assuming a Poisson model (*19*). No adjustments for multiple comparisons were made.

Results

The average sizes for the population at risk during 1980–1989 were as follows: region one, 725,076 men and 743,567 women; region two, 87,313 men and 89,359 women; region three, 88,985 men and 90,511 women; and region four, 1,066,913 men and 1,127,627 women. Age-standardized cancer mortality rates and ratios for 1980–1989 are presented separately for men and women, comparing crop regions one, two, and three to region four (Tables 1 and 2). In general, being a resident of crop regions one, two, or three had a beneficial effect as far as overall cancer mortality was concerned. Overall mortality from all cancers was significantly decreased in these crop regions as compared to region four. However, increased SRRs were observed for the following cancer sites in men: lip (region one); prostate (region three); thyroid (region three); and bone, including jaw (region three). These results were further analyzed by calculating the SRR for age categories <65 and ≥65, provided five or more deaths were reported for the specific age subcategory. The following SRRs were observed, listed by cancer site, region, and age category: 1) lip, region one, ≥65 years, SRR = 2.55 [95% confidence interval (CI), 0.95–6.80]; 2) prostate, region three, <65 years, SRR = 1.01 (CI, 0.65–1.58) and ≥65 years, SRR = 1.13 (CI, 1.01–1.27); 3) thyroid, region three, ≥65 years, SRR = 3.17 (CI, 1.30–7.76); 4) bone, including jaw, region three, <65 years, SRR = 2.97 (CI, 1.22–7.28).

Increased SRRs observed for women were nasopharynx (region one), eye (region three), and non-Hodgkin's lymphoma (region two). A breakout similar to that for the men by age category gave the following results: 1) nasopharynx, region one, ≥65 years, SRR = 4.28 (CI, 1.31–13.96); 2) non-Hodgkin's lymphoma, region two, <65 years, SRR = 1.48 (CI, 0.97–2.27) and ≥65 years, SRR = 1.28 (CI, 1.02–1.61). The number of cases reported for cancer of the eye was too small to be further categorized by age.

Significantly decreased SRRs were observed for several cancer sites in crop regions one, two, and three. Mortality from cancer of the trachea, bronchus, or lung was significantly decreased in both men and women in each of the three crop regions. Other smoking-related cancers such as cancer of the oral cavity, including tongue and larynx, for both men and women were either significantly decreased or similar as compared to region four. Other significantly decreased SRRs were noted in men for cancer of the esophagus, large intestine, liver and gall bladder, pancreas, kidney and ureter, bladder and other urinary organs, and connective and soft tissue. In women significant decreases were noted for cancer of the esophagus, pancreas, breast, ovary, and fallopian tube. Because the purpose of this study was to investigate excess cancer mortality in the crop regions, we did not further analyze these cancers with significantly decreased rates by age subcategory.

For children 0–14 years of age, no significant increases were observed for any of the cancer sites where five or more cases were reported (Table 3).

Discussion

The NCHS cancer mortality database provided an inexpensive and quick method to investigate the potential association between pesticide exposure and cancer mortality (*17*). The different ecologic systems, crop production characteristics, and the relative homogeneity of the population of Minnesota provide an opportunity to compare pesticide use patterns and health end points of interest within the borders of one state. By contrast, where these conditions do not exist, crude pesticide exposure assessments are unlikely to contribute to our current understanding of possible associations between pesticide exposure and cancer (*9*). Further, singular pesticide exposure effects may only be testable in laboratory animals. Residents of agricultural communities are typically exposed to a mixture of pesticides, which may interact differently within the exposed host. Some of the cancers observed in excess in the agricultural regions in the present study (lip, prostate, lymphoma), although not consistent for the three regions or for both genders, are in agreement with results from more detailed studies of men and women working in agriculture and exposed to agricultural pesticides in the north central United States (*9*). However, some notable exceptions were identified in male residents of region three. The present study showed an increased mortality for cancer of the bone and thyroid in adult males in northwestern Minnesota.

Few reports are available in the literature about these rare cancers in association with pesticides. In a 1993 study of male and female farmers from 23 states in the United States, Blair et al. (*10*) observed an excess of bone and thyroid cancer mortality among white male farmers in the central and southern states. Although these results were attributed to chance by Blair et al. (*10*), our findings for males (not females) appear to be consistent with their results. Further, in a mortality study of workers exposed to chlorophenoxy herbicides and chlorophenols, a significant excess of malignant thyroid cancer was observed for men (*20*). Altered thyroid hormone status in humans has been associated with exposure to dioxin, a contaminant of chlorophenoxy herbicides (*21*). A Norwegian study on cancer risk factors in men and women working in agriculture reported a twofold increase in thyroid cancer incidence in women working in orchards or greenhouses (*22*). Routine treatment of thyroid cancer is notably

Table 2. Cancer mortality rate ratios for white females during 1980–1989, comparing agricultural regions one, two, and three to region four[a]

	Region four		Agricultural regions			
Cancer site (*ICD-9* code)	Count	Rate	Region	Count	Rate	SRR (CI)
Salivary gland (142)	22	0.15	1	13	0.13	0.90 (0.44–1.87)
Nasopharynx (147)	6	0.05	1	14	0.15	3.35 (1.20–9.31)**
Oral cavity, including tongue (141, 143–146, 148, 149)	185	1.29	1	76	0.71	0.55 (0.41–0.74)*
			2	8	0.44	0.34 (0.15–0.77)*
			3	12	0.92	0.71 (0.37–1.36)
Esophagus (150)	212	1.39	1	88	0.83	0.59 (0.46–0.77)*
			2	13	0.62	0.45 (0.25–0.79)*
			3	9	0.48	0.34 (0.17–0.69)*
Stomach (151)	549	3.23	1	334	2.98	0.92 (0.80–1.07)
			2	61	3.07	0.95 (0.70–1.29)
			3	46	3.07	0.95 (0.68–1.33)
Large intestine (153, 159)	2,237	14.04	1	1,485	13.90	0.99 (0.92–1.06)
			2	286	14.70	1.05 (0.91–1.20)
			3	206	13.35	0.95 (0.82–1.11)
Rectum (154, excluding 154.3)	329	1.99	1	195	1.71	0.86 (0.71–1.04)
			2	34	1.83	0.92 (0.62–1.38)
			3	38	2.26	1.14 (0.79–1.65)
Liver, gallbladder, including bile ducts (155, 156)	536	3.46	1	340	3.29	0.95 (0.82–1.10)
			2	57	3.26	0.94 (0.70–1.28)
			3	63	4.36	1.26 (0.95–1.67)
Pancreas (157)	1,136	7.38	1	646	6.10	0.83 (0.75–0.92)*
			2	129	7.14	0.97 (0.79–1.18)
			3	107	7.15	0.97 (0.78–1.20)
Nose, nasal cavities, middle ear, accessory sinuses (160)	28	0.20	1	15	0.12	0.62 (0.32–1.19)
Larynx (161)	56	0.44	1	16	0.17	0.39 (0.22–0.71)*
Trachea, bronchus, lung (162, 163, 165)	3,145	23.77	1	1,434	16.49	0.69 (0.65–0.74)*
			2	200	14.26	0.60 (0.51–0.70)*
			3	186	15.55	0.65 (0.56–0.76)*
Breast (174, 175)	3,694	27.27	1	2,465	27.56	1.01 (0.96–1.07)
			2	392	27.31	1.00 (0.89–1.12)
			3	288	23.24	0.85 (0.75–0.97)*
Cervix uteri (180)	257	1.92	1	146	1.68	0.88 (0.71–1.09)
			2	15	1.34	0.70 (0.39–1.24)
			3	18	1.90	0.99 (0.60–1.63)
Chorion, uterus (179, 181, 182)	555	3.72	1	344	3.26	0.88 (0.76–1.01)
			2	71	4.22	1.13 (0.87–1.48)
			3	43	3.40	0.91 (0.66–1.27)
Ovary, fallopian tube, broad ligament (183)	1,281	9.48	1	729	7.96	0.84 (0.76–0.92)*
			2	94	6.17	0.65 (0.52–0.82)*
			3	110	8.46	0.89 (0.72–1.10)
Kidney, ureter (189, excluding 189.3)	378	2.49	1	234	2.53	1.01 (0.85–1.20)
			2	39	2.49	1.00 (0.70–1.42)
			3	48	3.43	1.37 (0.99–1.91)
Bladder, other urinary organs (188, 189.3)	314	1.84	1	190	1.54	0.84 (0.69–1.02)
			2	25	1.24	0.68 (0.44–1.05)
			3	36	2.03	1.11 (0.76–1.61)
Malignant melanoma (172)	191	1.40	1	126	1.41	1.01 (0.79–1.28)
			2	25	1.79	1.28 (0.81–2.03)
			3	16	1.46	1.05 (0.61–1.79)
Nonmelanoma skin (173, 154.3)	72	0.46	1	37	0.34	0.73 (0.48–1.13)
			3	6	0.45	0.97 (0.41–2.29)
Eye (190)	10	0.07	1	6	0.06	0.84 (0.28–2.49)
			3	5	0.42	5.77 (1.90–17.50)**

continued, next page

successful for the more common forms of this disease, with a 5-year survival rate of over 90% (*23–25*). Clearly mortality data underestimate the number of people with thyroid cancer in this region, and could reflect variation in quality or availability of care, not just variation in mortality from thyroid cancer. On the other hand, variation in the form of the disease could be an alternative explanation for these results. In an ongoing study of pesticide appliers residing in region three, 4 of the 140 appliers showed clinically significant abnormalities of thyroid function (*26*). Two were under medical care for hypothyroidism, two were not. These anecdotal data suggest underutilization of medical care services.

In terms of etiology, the causative agent for the observed increase in thyroid cancer mortality is uncertain. To date, no pesticides have been proven to be carcinogenic to the human thyroid (*25,27*). Heavy use of chlorophenoxy herbicides in western Minnesota creates concern for elevated dioxin levels in this population. In addition, fungicides such as maneb, mancozeb, propiconazole, and supertin, widely applied to wheat, potatoes, and sugar beet crops, present a potential health hazard. Mancozeb is most commonly applied to potatoes, which are a major crop in region three. In addition, potatoes are also treated with maneb and blite-out, a mixture of maneb and triphenyltin. Both mancozeb and maneb are ethylenebisdithiocarbamates (EBDC). The major metabolite of these products is ethylenethiourea (ETU), a known cause of thyroid cancer in rats. Houeto et al. (*28*) presented a study summarizing the effects of EBDC and ETU. Mechanistically, ETU decreases thyroxine and increases thyroid-stimulating hormones, as well as causes thyroid and liver neoplasms in rodents. ETU is a thyroid peroxidase inhibitor in rodent studies, disrupting the thyroid–pituitary homeostasis (*25,27*). Besides their effect on the thyroid, EBDCs are also teratogenic in rodents, causing damaging effects in the gonads of both male and female rats, which

Table 2. *continued*

	Region four		Agricultural regions			
Cancer site (*ICD-9* code)	Count	Rate	Region	Count	Rate	SRR (CI)
Brain, other parts of nervous system (191, 192)	512	4.04	1	303	3.67	0.91 (0.78–1.05)
			2	38	3.11	0.77 (0.54–1.10)
			3	49	4.14	1.02 (0.75–1.40)
Thyroid (193)	61	0.38	1	38	0.36	0.94 (0.61–1.45)
			2	5	0.17	0.44 (0.17–1.15)
			3	8	0.45	1.18 (0.54–2.62)
Thymus and other endocrine glands (194, 164.0)	39	0.36	1	21	0.26	0.72 (0.42–1.26)
Bone, including jaw (170)	39	0.29	1	32	0.36	1.22 (0.74–2.00)
			2	7	0.51	1.74 (0.67–4.54)
Connective and soft tissue (171, 164.1)	122	0.92	1	87	0.98	1.07 (0.80–1.43)
			2	20	1.45	1.58 (0.93–2.69)
			3	14	1.14	1.24 (0.69–2.23)
Hodgkin's disease (201)	85	0.58	1	47	0.55	0.95 (0.66–1.38)
			2	7	0.39	0.67 (0.28–1.59)
			3	9	0.59	1.02 (0.48–2.14)
Lymphosarcoma, reticulum cell sarcoma, including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	804	5.23	1	549	5.32	1.02 (0.91–1.14)
			2	117	7.04	1.35 (1.09–1.66)**
			3	70	4.96	0.95 (0.73–1.24)
Multiple myeloma (203, excluding 203.1)	386	2.40	1	228	2.28	0.95 (0.80–1.13)
			2	52	3.23	1.35 (0.98–1.85)
			3	35	2.29	0.95 (0.66–1.38)
Leukemia (204–208, 202.4, 203.1)	775	5.16	1	538	5.19	1.01 (0.90–1.13)
			2	80	5.06	0.98 (0.75–1.28)
			3	82	5.76	1.12 (0.87–1.43)
Secondary, site unspecified, not previously listed (152, 158, 159.2–159.9, 164.2–164.9)	1,459	9.16	1	833	7.86	0.86 (0.78–0.94)*
			2	157	8.63	0.94 (0.78–1.14)
			3	140	9.04	0.99 (0.82–1.19)
All cancers (140–208)	19,476	134.54	1	11,610	119.77	0.89 (0.87–0.91)*
			2	1,946	120.71	0.90 (0.85–0.95)*
			3	1,660	121.58	0.90 (0.86–0.95)*

Abbreviations: *ICD-9, International Classification of Diseases, 9th Revision* (World Health Organization, Geneva); SRR, standardized rate ratio; CI, 95% confidence interval. Rates per 100,000 are age-adjusted.
[a]Provided at least five deaths are reported in each of the two groups being compared.
*Significantly decreased SRR.
**Significantly increased SRR.

Table 3. Cancer mortality rate ratios for white children during 1980–1989, comparing agricultural regions one, two, and three to region four[a]

	Region four		Agricultural regions			
Cancer site (*ICD-9* code)	Count	Rate	Region	Count	Rate	SRR (CI)
Boys						
Brain, other parts of nervous system (191, 192)	27	1.17	1	12	0.65	0.56 (0.28–1.10)
Thymus and other endocrine glands (194, 164.0)	7	0.28	1	6	0.30	1.08 (0.36–3.23)
Lymphosarcoma, reticulum cell sarcoma, including other lymphoma (159.1, 200, 202.0, 202.1, 202.8, 202.9)	10	0.42	1	6	0.35	0.83 (0.30–2.29)
Leukemia (204–208, 202.4, 203.1)	36	1.53	1	26	1.44	0.94 (0.57–1.56)
			2	6	3.10	2.02 (0.85–4.81)
All cancers (140–208)	98	4.18	1	62	3.42	0.82 (0.59–1.13)
			2	12	6.21	1.49 (0.81–2.71)
			3	13	5.99	1.43 (0.80–2.56)
Girls						
Brain, other parts of nervous system (191, 192)	22	0.97	1	12	0.75	0.77 (0.38–1.55)
Thymus and other endocrine glands (194, 164.0)	10	0.43	1	7	0.37	0.86 (0.33–2.26)
Leukemia (204–208, 202.4, 203.1)	19	0.85	1	14	0.76	0.89 (0.44–1.77)
All cancers (140–208)	64	2.83	1	48	2.77	0.98 (0.67–1.43)
			2	8	4.20	1.49 (0.71–3.10)
			3	5	2.50	0.88 (0.35–2.20)

Abbreviations: *ICD-9, International Classification of Diseases, 9th Revision* (World Health Organization, Geneva); SRR, standardized rate ratio; CI, 95% confidence interval. Rates per 100,000 are age-adjusted.
[a]Provided at least five deaths are reported in each of the two groups being compared.

result in decreased fertility and malformations in the offspring (*28*).

Few studies have reported possible human health effects from EBDCs, although these pesticides have been classified as probable human carcinogens (*29*). Von Meyer (*30*) reported an increasing trend in the incidence of human liver and thyroid cancer in regions in four states of the United States where EBDCs were used, but these increases were not statistically significant. In a recent study, Steenland et al. (*31*) reported increased thyroid-stimulating hormone levels as well as an increase in sister chromatid exchanges and chromosome translocations in heavily exposed pesticide sprayers applying EBDCs to tomato crops in Mexico.

In addition to pesticides, residents in region three are also exposed to radon in their drinking water. Groundwater from 60% of the wells examined by the U.S. Geologic Survey contained radon in excess of 300 pCi/l (*32*). The level of radioactive iodine in this water, long associated with thyroid and other cancers, is unknown at the moment.

Cancer of the thyroid generally occurs more frequently in women than in men (*25*). The overall U.S. 1980–1989 mortality rates for thyroid cancer were 0.32 and 0.40 per 100,000 for men and women, respectively, with a resulting M:F ratio of 1:1.3. The M:F ratios for the 1980–1989 mortality rates for thyroid cancer in the agricultural regions of Minnesota were region one, 1:2.4; region two, 1:0.4; region three, 1:0.6; and region four, 1:1.5. The increased thyroid cancer mortality observed among men in regions two and three, as compared to women in the same regions, could be related to environmental or occupational exposures.

We observed a twofold increase in mortality from bone cancer for men under age 65 in region three. A firm link between bone cancer and pesticide exposures has not been shown. Results for mortality from these rare cancers (bone, thyroid) should be confirmed by cancer incidence and case–control studies.

In addition to thyroid cancer, cancer mortality in region three was increased for other endocrine glands as well—testicular cancer in adult men and a combined group of cancers called "thymus and other endocrine glands" in boys 0–14 years of age. Although these results were not included in Tables 1 and 3 (only four deaths were reported for each category), they are worth noting because the thyroid, testis, thymus, and other endocrine glands are organs susceptible to endocrine disruption. The four deaths from testicular cancer resulted in a rate of 0.48 per 100,000 in region three, almost a twofold increase over the the rate of 0.25 per 100,000 in referent region four. The rates in regions one and two were 0.39 (n = 32) and 0.06 (n = 1), respectively. The four deaths for cancer of the thymus and other endocrine glands resulted in a rate of 1.78 per 100,000, which is more than a sixfold increase over the rate of 0.28 per 100,000 in region four, with seven cases reported. Among the four boys in region three, three died between 0 and 4 years of age and one died between 5 and 9 years of age. Regions one and two reported, respectively, six deaths (0.30 per 100,000) and one death (0.44 per 100,000) for boys 0–14 years of age for this group of cancers. The "other endocrine glands" include adrenal gland, parathyroid gland, pituitary gland and craniopharyngeal duct, pineal gland, carotid body, aortic body and other paraganglia, and unspecified endocrine glands. Because of human subject concerns, we have not identified the exact *International Classification of Diseases, Revision 9* (World Health Organization, Geneva) codes for this small group of subjects. Generally, cancers occurring this early in life may be explained by prenatal exposure of either parent to mutagenic agents or by genetic predisposition (*33*).

Studies of women exposed to pesticides are fewer in number than those of men, probably because they are presumed to have less frequent or lower exposures to pesticides (*9,11*). However, agricultural use of pesticides is only a partial measure of total personal exposure. Other contributing factors are exposure to contaminated house dust, carpet, clothing, soil, etc. (*9*). The results from our study and from other studies indicate that increased cancer risks for people engaged in farming or living in farming communities are similar for men and women for some cancers, but may be dissimilar for others. Dissimilarity in total personal exposure may account for some of the gender dissimilarities in cancer risk. Increased mortality risks observed among women (but not men) in the current study are cancer of the nasopharynx and eye and non-Hodgkin's lymphoma. Increased mortality from cancer of the nose and nasal cavity has been reported for workers exposed to chlorophenoxy herbicides (*20*). Increased risk for nasopharyngeal cancer has been reported for occupational exposures to chlorophenoxy herbicides (*34*).

Increased cancer of the eye has been reported for rural populations, and is thought to be related to exposure from sunlight (*22,35*). In our study, mortality from eye cancer was significantly increased for women (but not men) in region three.

The protective effect observed among residents of the agricultural regions for smoking-related cancers (trachea, bronchus, lung, larynx, oral cavity) and all cancers combined is consistent for all three regions and for both genders. The current study confirms that lifestyle-mediated cancers are in deficit in the farming community (*9,22*).

With respect to known agriculturally associated cancers, not unexpectedly, the different crop patterns and ecology for each of the three agricultural regions gave rise to a somewhat different cancer spectrum. Differences in agricultural pesticide use patterns, types of pesticides used, and regional groundwater contaminant levels are a primary concern. Increased mortality from relatively rare cancers (thyroid, bone, testis, thymus, and other endocrine glands), as occurred in region three, raises a number of etiologic concerns and warrants further investigation. Epidemiologic and laboratory based population studies are underway to elucidate factors involved in the cancer mortality and birth defect excesses cited in these ecologic studies.

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